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Amantadine Aerosol in Humans

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Seven well volunteers and three patients with a naturally occurring influenza A/USSR/77 (H1N1)-like infection were given amantadine by small-particle aerosol with a Collison generator modified for this purpose. Inhalation periods for the volunteers were increased on consecutive weekends from 15 min to 1 h, 4 h, 9 h, and 2 consecutive days of 6 h each. The particle size was 1.2-μm mass median diameter, and the concentration of inhaled aerosol ranged from 47 to 75 μg/liter. Estimates of retained doses in 9 h were 74 to 149 mg. About two-thirds of the dose was recovered in the urine. Pulmonary function studies did not vary significantly from base-line values and were within a normal range for five of seven volunteers. Two volunteers with a moderate reduction in mid-maximal flow before exposure had a total of three episodes of coughing and wheezing associated with moderate reductions in mid-maximal flow values. These episodes cleared spontaneously or improved promptly after isoproterenol therapy. The patients with influenza tolerated the treatment well and recovered promptly.

Amantadine is currently used in the prevention and treatment of influenza A by the oral route in doses of 100 mg twice daily in adults. Given prophylactically, amantadine reduces the frequency and the extent of subsequent illness (6); therapeutically, it reduces symptoms and speeds defervescence but only slightly reduces the frequency and titer of virus recovery (7). In personal experience (V.K.) variable results were obtained with high oral doses of amantadine in the treatment of patients with influenzal pneumonia.

It seemed possible that delivery of amantadine to the surface of the respiratory tract in small-particle aerosol might improve its therapeutic effectiveness. Acting on that premise, United States Army scientists developed equipment to provide for extended periods of administration of small-particle aersol (13) and tested the device with experimental influenza infections in mice (11). They found that amantadine and rimantadine treatment by small-particle aerosol (23.5 h/day) started 72 h after inoculation, when virus titers in the lung were near maximal, led to survival of approximately two-thirds of treated animals in contrast to less than 10% survival in controls. About 15% of mice given equivalent doses of amantadine intraperitoneally survived. These differences were highly significant.

We confirmed the findings of the Fort Detrick workers in mice and further showed that survival rates after 8 h of continuous treatment were nearly identical to the longer 23.5-h treatment (12). On that basis, it appeared that amantadine given by small-particle aerosol might be highly effective in treatment of the disease in humans and in particular might benefit patients with influenzal pneumonia for whom no effective treatment is available.

Limited studies of amantadine aerosol treatment in humans were made by Hayden and his associates (F. G. Hayden, W. J. Hall, R. G. Douglas, Jr., and D. M. Speers, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 18th, Atlanta, Ga., abstr. no. 485, 1978). They treated patients acutely ill with influenza A infection with amantadine aerosol for 20 min three times daily for 4 days. Recovery from respiratory illness was accelerated in treated patients, but there was no effect on systemic illness or virus shedding. Although the concentration of drug used by these authors was similar to that of our studies, the dosage period was much shorter, which may explain the lack of effect of treatment.

The present report describes results that indicate that amantadine in small-particle aerosol is rapidly absorbed by this route of administration and is generally well tolerated.

MATERIALS AND METHODS

Aerosol apparatus. The continuous-flow, modified Collison nebulizers were of the Fort Detrick design (13). Briefly, the units consist of Collison nebulizers attached to a reservoir of drug solution whose flow through the nebulizer is controlled by a peristaltic pump. Inhalations were administered intranasally through a rubber aviator mask. The reservoir contained 15 mg of amantadine per ml in distilled water, and the concentration of amantadine in aerosol ranged

from 47.5 to 75.5 μg/liter. The mass median diameter of aerosol particles was quite uniformly about 1.2 μm. The apparatus and its operating characteristics are described elsewhere (12).

Gas chromatographic assay of amantadine. Amantadine was assayed in urine with a sensitivity of less than 1 μg/ml by using a column designed for assay of amphetamines (M. J. Stumph and M. W. Noall, Clin. Chem, in press). The method is not suitable for assay of amantadine in blood. In brief, it is a gas-liquid chromatographic method that uses β-phenylethylamine as an internal standard. The urine sample is made alkaline and extracted with 0.3 ml of chloroform. After centrifugation the aqueous layer is aspirated, and a portion of the organic layer is injected directly into the gas chromatograph. Concentration and instrument response are linearly related between 2 and 125 μg/ml. The limit of detection is 0.5 μg/ml. Mean analytical recovery is 97%.

Volunteers. A description of the seven persons who volunteered is given in Table 1. All were young adults; three were women, and four were men. History and physical examinations were normal except for the presence of mild bronchial asthma, not previously diagnosed, in a young woman (volunteer 3) who smoked one pack of cigarettes per day, the only smoker in the group. After discussing with her the possible hazards, we decided to proceed cautiously with the experiment. One other subject (volunteer 7) had a reduced value for mid-maximal flow (FEF25-75). Some months later, she reported a bronchospastic attack after exposure to flea powder.

The following tests were performed on all volunteers: routine blood and urinalysis, chest roentgenogram, electrocardiogram, SMA-13, serum electrolytes, and serum electrophoresis. All tests were within normal limits except an eosinophilia of 11% in volunteer 3 who had mild bronchial asthma. In most instances, blood counts and blood chemical studies were repeated near the end of the study. None had changed significantly.

Patients. After the studies in normal volunteers, three patients with naturally occurring influenza A/USSR/77 (H1N1)-like infection in January, 1979, volunteered to participate in the study.

Pulmonary function testing. Testing was begun within 30 min after completion of aerosol inhalations. Basic spirometry was performed on an Ohio 840 rolling-seal spirometer. Reduction of the raw data was facilitated by an online PDP-12 analog digital computer programmed to yield forced vital capacity (FVC), volume expired in 1s (FEV_1), FEF25-75, and flows at 25, 50, and 75% of the vital capacity. For each determination, forced expiratory flows were repeated a minimum of three times. Data for interpretation were selected by the criteria outlined by the Snowbird Conference (Conference on Standardization of Spirometry, Snowbird, Utah, 18 January 1977). Lung volumes and airway resistances were determined by shallow panting technique in an Ohio 3000 constant-volume body plethysmograph. Single-breath diffusion capacity (DL_{CO}) was determined with a PK Morgan Analyzer with 9.96% helium, 0.33% CO, and 20% O_2 as a test gas. Predicted normal values for FVC, FEV_1, FEV_1/FVC, and FEF25-75 were those of Morris et al. (10); values for total lung capacity and FRC for women were those of Goldman and Becklake (4) and those for men were from Boren et al. (1). Predicted normal values for DL_{CO} were those of Burrows et al. (2). The percentage of improvement in forced expiratory flows at 25% of the vital capacity ($\Delta \dot{V}_{max}25$) was determined with the subject breathing 80% helium–20% oxygen as compared with breathing air. The $\dot{V}_{max}25$ breathing air or the He-O_2 mixture was averaged from three forced expiratory flows with each gas where the FVC varied no more than 3%.

Before starting the inhalation challenges, which were performed on successive weekends, the volunteers underwent complete base-line testing with spirometry, plethysmography, and DL_{CO} measurements. At the first session they received one 15-min inhalation each of amantadine and saline in randomized order. This was repeated on the second weekend with 1-h inhalations of amantadine and saline. On the third weekend, before and just after a 4-h inhalation of amantadine, spirometry, lung volumes, and DL_{CO} were measured. During subsequent weekends, four subjects (including the reactor volunteer, 7) inhaled amantadine aerosol 6 h each day for 2 days, and four (including the reactor volunteer, 3) inhaled amantadine aerosol for a single 9-h period. Before and after these longer inhalation periods, all subjects underwent the complete pulmonary function testing described above.

RESULTS

The subjects' tolerance to amantadine nebulization was generally good. There was no evi-

TABLE 1. *Description of volunteers*[a]

Volunteer	Age	Sex	Race	Wt (pounds)	Ht (inches)	V_e (liters/min)	Physical status
1	22	M	W	162 (73)	75 (191)	6.8	Normal
2	19	M	W	160 (73)	73 (185)	8.3	Normal
3	23	F	W	120 (54)	62 (157)	7.2	Mild bronchial asthma
4	24	M	W	195 (88)	75 (191)	9.6	Normal
5	20	M	B	127 (58)	66 (168)	4.7	Normal
6	27	F	W	114 (52)	63 (160)	4.7	Normal
7	29	F	W	106 (48)	60 (152)	6.8	Normal

[a] Volunteers 2, 4, and 5 participated in the 9-h study and volunteers 2, 5, and 6 participated in the two 6-h studies. Volunteer 6 missed the first 15-min saline inhalation.

[b] Figures in parentheses are approximate metric equivalents in kilograms.

[c] Figures in parentheses are approximate metric equivalents in centimeters.

dence of anaphylaxis, and vital signs remained normal. No subjects experienced nausea, vomiting, anorexia, headache, or other generalized symptomatology. Two subjects, however, developed signs of reversible bronchoconstriction, which is described in detail later. During the longer inhalation periods, a fine white precipitate accumulated within the aviator mask and on the face. No skin reactions were noted. However, several subjects complained of a mild burning or itching sensation in the nares and an occasional sneeze. This was accompanied by a very mild erythema of the nasal mucosa. This mild nasal irritation was never severe enough to require discontinuation of the inhalation. It appeared to be a nonspecific superficial reaction and was quickly resolved.

Pulmonary function studies. Base-line pulmonary functions showed very little variation between testing periods for the normal volunteers. The standard deviations of these base-line studies are shown in Table 2. FVC and FEV_1 were reproduced with less than 4% variation. The FEF25-75 tests varied no more than 8%. The asthmatic subject showed slightly more variable base-line values, but FEV_1 and FVC were reproducible to within 8% and the FEF25-75 to within 15%.

The results of spirometric studies after amantadine inhalation in five volunteers are shown in Fig. 1. The responses of the two volunteers who experienced reactions will be described separately. In Fig. 1 the vertical rectangles enclose results of different days of study. The two 6-h inhalations were performed on consecutive days. The results are plotted to show the percent change from the base-line values determined for each volunteer before each challenge. Lines connect paired values for the same patient. The variation encountered was within the reproducibility of the tests, and the mean values showed even less variation from the base line. One subject (volunteer 5) showed an improvement in FEF25-75 of 20% after a 15-min saline inhalation and maintained this improvement after amantadine inhalation. His subsequent base-line FEF25-75s were higher than those for the first test, and he did not demonstrate any consistent bronchodilatory response to amantadine.

Measurements of airway resistance, DL_{CO}, and small airway reactivity (percent $\Delta \dot{V}_{max}25$) were made before and after the 6- and 9-h inhalations. Individual values after inhalation showed only minor variations from those obtained earlier, and the means before and after were nearly identical.

Two subjects with abnormalities on base-line testing demonstrated a mild, sporadic bronchial reactivity to inhaled amantadine. The responses of the asthmatic (subject 3) are depicted in detail in Fig. 2. After the initial 15-min amantadine challenge, she remained asymptomatic but demonstrated a significant fall in the FEV_1 and FEF25-75. After isoproterenol inhalation, her function rapidly improved to better than base line. She tolerated 1- and 4-h challenges with only minimal alteration in FEF25-75. However, during a 9-h amantadine inhalation, she developed wheezing and a nonproductive cough after 8 h, 15 min of inhalation that was promptly relieved by inhalation of isoproterenol. The other reactor (volunteer 5) showed a similar pattern of response with a small asymptomatic fall in FEF25-75 after 1 h of amantadine and two

TABLE 2. *Observed and expected values of pulmonary function tests of volunteers*

Volunteer	FVC		FEV_1		FEV_1/FVC		FEF 25-75		TLC[b]	
	Observed	Expected	Observed	Expected	Observed	Expected	Observed	Expected	Observed	Expected
1 ($N = 5$)	6.63 ± 0.05	6.30	5.29 ± 0.08	4.93	79.8 ± 1.5	78.0	4.80 ± 0.15	5.04	8.46	7.56
2 ($N = 4$)	5.80 ± 0.20	5.00	4.84 ± 0.26	4.71	85.7 ± 4.3	94.0	4.82 ± 0.26	4.89	7.73	6.37
3 ($N = 4$)	4.04 ± 0.23	3.72	2.90 ± 0.20	3.01	71.8 ± 3.0	81.0	2.15 ± 0.28	3.56	4.67	4.77
4 ($N = 4$)	6.33 ± 0.18	6.25	5.27 ± 0.16	4.87	83.5 ± 1.6	78.0	5.84 ± 0.37	4.95	8.07	7.56
5 ($N = 5$)	3.56 ± 0.07	4.51	3.36 ± 0.13	3.75	94.8 ± 2.5	83.0	4.75 ± 0.40	4.71	5.07	5.2
6 ($N = 5$)	3.33 ± 0.09	3.74	3.03 ± 0.09	3.00	90.6 ± 2.1	85.0	3.35 ± 0.27	3.56	5.53	4.94
7 ($N = 4$)	3.18 ± 0.05	3.35	2.62 ± 0.02	2.68	82.6 ± 0.96	80.0	2.58 ± 0.05	3.28	3.57	4.32

[a] Specific conductance (SGaw) was normal in all volunteers except volunteer 3 where it was reduced (0.06 observed, >0.2 predicted).

[b] TLC, Total lung capacity.

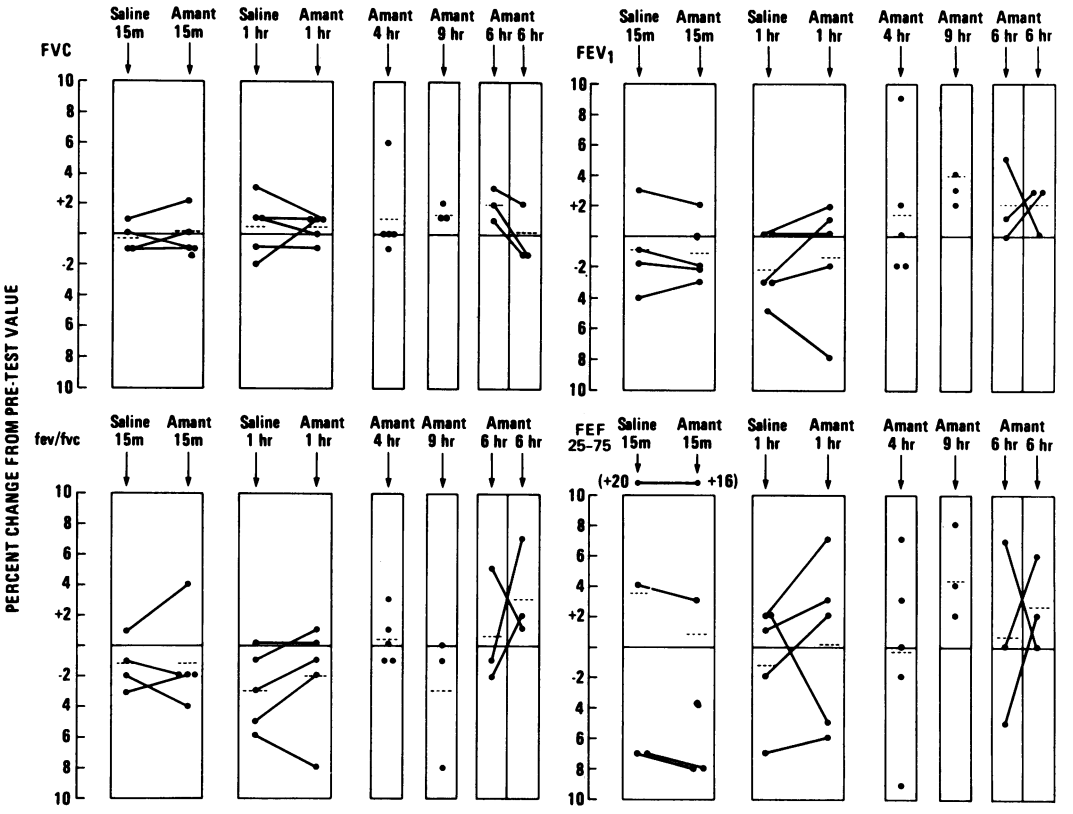

FIG. 1. *Response of five volunteers to inhalations of small-particle aerosol. Results of the four tests are shown as percent change from the base-line value (pretest) for each test which has been arbitrarily adjusted to 100%. The mean and standard deviation for base-line values for each volunteer are shown in Table 2, and the results are quite uniform. Mean values are indicated by dashed lines.*

subsequent symptomatic episodes associated with a fall in FEF25-75 after 2 h, 5 min and 4 h, 12 min of amantadine inhalation. These changes reverted to base line within 1 h without treatment. A later 4-h inhalation of saline caused no reaction.

Tolerance of patients with influenza to aerosol treatment. In January 1979 three young adults with influenza A/USSR/77 (H1N1)-like infection were treated with amantadine small-particle aerosol. They had been ill 6, 24, and 36 h before treatment was started. Amantadine aerosol in the same concentration as that given to the volunteers was administered in 2- to 4-h courses 10 to 11 h daily for 3 days.

Recovery was rapid in all cases, with rapid defervescence and clearing of symptoms. Pulmonary function studies showed mild restrictive ventilatory defects in two patients on admission. In one patient there was significant improvement by the end of treatment; in the other, ventilatory restriction was still present 3 weeks later. These changes are considered possibly due to influenza, but a preexisting abnormality must be considered. Despite acute influenza there was no evidence of irritation of the respiratory tract of these patients by amantadine inhalations. A description of the course of the patient whose respiratory defect improved during treatment is shown in Fig. 3.

Excretion of amantadine in urine. Six volunteers inhaled aerosol containing amantadine for 15 min. Forty-five minutes from the start of the 15-min period, the average concentration of amantadine in urine was 4.2 ± 4.6 μg/ml. The concentration in urine was measured again in two of the volunteers after 75 min, and the average was 1.2 ± 0.9 μg/ml. This indicates a rapid and efficient absorption of the drug during the brief aerosol exposure. Table 3 shows the urine concentrations and amount excreted during and after 9 h of amantadine aerosol inhalation. There was a gradual increase in concentration and total excretion during three consecutive 3-h collections during inhalation, whereas the major excretion occurred during the 9 to 33 h

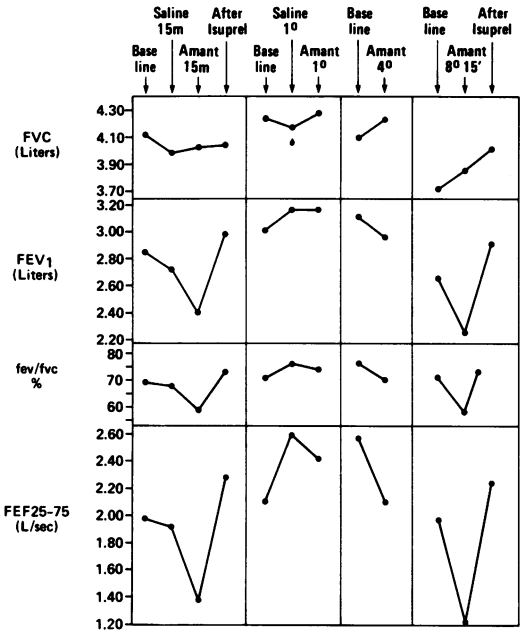

FIG. 2. *Changes in four pulmonary function tests of volunteer 3 with mild bronchial asthma after inhalations of saline and amantadine in aerosol. The only detectable reaction, manifested by moderate wheezing and cough, occurred after 8 h, 15 min of inhalation of amantadine aerosol. Changes similar to those associated with the reaction, but without symptoms, occurred following the 15-min exposure to amantadine.*

after inhalation. In the more than 33-h period, excretion was greatly reduced.

Individual values for urinary excretion are shown in Table 4 along with data on aerosol dosage of amantadine. Despite some variation in collection periods, more than one-half of the estimated retained dosage in most volunteers was recovered. Volunteer 5, who took part in both the 9-h and the two 6-h studies, yielded 99 and 110% recovery. This apparent inconsistency probably indicates that the figure of 53% retention is not generally applicable and that this volunteer was more efficient at absorbing amantadine from aerosol than were the other volunteers. This is probably preferable to suggesting that his urinary excretion of absorbed aerosol is more complete than the others.

DISCUSSION

These studies indicate that amantadine can

TABLE 3. *Urinary excretion after a 9-h inhalation of amantadine small-particle aerosol*

No. of subjects	Time after start of inhalation (h)	Concn (μg/ml)	Excretion (mg/sample)
4	0–3	7.2 ± 4.9	2.1 ± 1.7
4	3–6	19.4 ± 11	5.9 ± 4.2
4	6–9	22.0 ± 11.3	7.6 ± 5.0
3	9–33	45.0 ± 18.2	48.0 ± 15.0
3	33+[a]	15.0 ± 5.2	11.5 ± 5.4

[a] This collection period was variable. See Table 4.

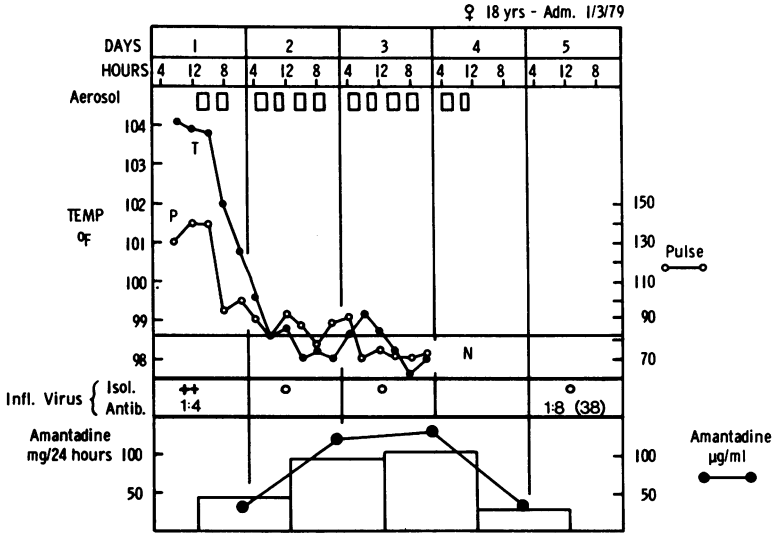

FIG. 3. *An 18-year-old female with acute influenza caused by A/USSR/77(H1N1)-like infection. On admission, the patient was profoundly prostrated; the pulse rate was 140/min, but the chest was clear and coughing was not severe. Temperature and pulse returned permanently to normal within 20 h after the start of treatment. Signs and symptoms cleared rapidly. The inhalations were well tolerated.*

TABLE 4. *Recovery in urine of amantadine administered by aerosol*[a]

Inhalation period	Volunteer	V_e (liters/min)	Amantadine aerosol concn[b] (μg/liter)	Duration of treatment (min)	Estimated retention (0.53, mg)[c]		Recovery in urine (mg)	Total period of urine collection (h)	Aerosol dose recovered in urine (%)
6 h, each of 2 days	1	6.8	70.2	360	91	189	144	73	76
		6.8	75.5	360	98				
	7	6.8	70.2	252[d]	64		36.4	78	57
	5	4.7	75.5	360	67.7	130.6	129.9	73	99
		4.7	70.2	360	62.9				
9 h	2	8.3	52.3	540	124		60.8	34	49
	3	7.2	50	495[d]	94		51.5	48	55
	4	9.6	54.3	540	149		89.4	32	60
	5	4.7	55.6	540	74.8		82.7	48	110

[a] During the 6-h inhalation, a 200-ml reservoir volume was used; during the 9-h inhalation a 300-ml reservoir volume was used. With the latter, the effect of evaporation on reservoir fluid concentration was less. Estimated retention (mg) = [V_e (liters/min) × concentration (μg/liter) × minute × 0.53]/1,000.

[b] Concentration taken at midpoint of inhalation period to compensate for increase in concentration due to evaporation of water in excess of aerosolized solute.

[c] See reference 12.

[d] Treatment terminated because of reaction.

be administered with reasonable safety via small-particle aerosol. Pulmonary function studies demonstrated no evidence of abnormalities after amantadine inhalation in five normal volunteers, and flow studies with helium-oxygen did not suggest any changes in the status of small airways in these subjects. Two others, the asthmatic and one asymptomatic subject, had mild episodes of bronchospasm after prolonged amantadine inhalation. In these two subjects, pulmonary function testing after amantadine confirmed an obstructive defect by a drop in the FEF25-75 and FEV_1. The reactions resolved spontaneously in less than 1 h or immediately upon isoproterenol inhalation. Volunteer 7, who twice reacted to amantadine inhalation, subsequently inhaled aerosolized saline for 4 h with no measurable effects, thus implicating amantadine as the offending agent. We feel that the bronchospastic reactions were secondary to a nonspecific irritant effect of the deposited amantadine. This was suggested by the appearance of reactions only after prolonged inhalation periods, as well as by the prompt and spontaneous resolution on discontinuing exposure. Were these late type reactions, as are seen in some forms of hypersensitivity asthma, we would not have anticipated such prompt reversibility.

At present we feel that amantadine may irregularly produce mild abnormalities in susceptible patients with reactive airways. Normal subjects tolerate amantadine inhalation extremely well. Recent studies have suggested that the airways of patients with influenza show increased bronchial reactivity to carbachol during the acute phase of the illness (9). The response of such patients to inhaled amantadine will need to be monitored closely. Inhalation periods of 2 to 4 h will probably reduce the frequency of adverse reactions. Furthermore, inhaled bronchodilators can be administered concurrently or prophylactically. And finally, therapy can immediately be abandoned if necessary. The current study did not include blood gas analysis after amantadine inhalation. Arterial gases could be determined in patients with influenza. We would do this only if there was a need for these data to provide optimum clinical supervision. If necessary, supplemental oxygen may be administered concurrently with the aerosol therapy.

We believe the majority of patients will tolerate several 2- to 4-h inhalations daily. Ten hours will provide a daily retained dose of amantadine of 100 to 150 mg. The currently recommended adult oral dose is 200 mg/day. The final aerosol dose will depend on therapeutic studies in humans. The pharmacological studies further confirm that inhaled amantadine is rapidly and efficiently absorbed. We feel that the potential benefits of therapy in patients with serious influenza infection outweigh the small risk of this form of therapy and that further investigation of inhaled amantadine in patients with influenza is warranted.

Theoretical and experimental studies of small-particle aerosol deposition in humans indicate that, with nasal breathing at the normal rate, 36% of 1.5-μm hygroscopic particles will deposit in the nose, 1% will deposit in the pharynx to secondary bronchi, 25% will deposit in tertiary

bronchi to respiratory bronchioles, and 21% will deposit in alveolar ducts (8). This totals 83% deposition of inhaled aerosol. With our 1.2-μm-diameter particles, deposition would be somewhat more than that. Another study showed a similar deposition pattern with only 53% total retention (5). We presume that a highly soluble, small molecule like amantadine is absorbed at about the same rate from all sites. Such a retention would be most appropriate for the treatment of influenza since the infection involves cells at all levels of the respiratory tract. Some of the drug deposited in the nasopharynx could also be swallowed and absorbed from the gastrointestinal tract. In a study of 2.5-μm-diameter radioactive particles inhaled through the mouth (3), the correction for material swallowed was only 4% of the total inhalation, a value of little consequence when compared with the amounts that deposit in the respiratory tract. This value would not differ greatly from that for the 1.2-μm-diameter particles employed in this study. We used the value of 53% deposition to determine estimated doses, but in view of the high percentage of estimated recoveries based on assay of the drug in the urine, we believe that the percentage deposition in the respiratory tract is higher than 53%. We propose to study these questions in greater detail.

The therapeutic trials with naturally occurring influenza are incomplete and were described to show lack of irritation of the respiratory tract by inhalations that deliver about two-thirds of the usually recommended oral dose of amantadine. It is currently the view that this mode of administration of amantadine might prove effective in the treatment of influenzal pneumonia. We believe that the present studies justify continued therapeutic trials to determine the value of the treatment.

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